Addendum to the ATSDR Toxicological Profile for Manganese
September 21, 2010

- An MRL of 0.04 µg manganese/m^3 (manganese in respirable dust) has been derived for chronic inhalation exposure (365 days or more) to manganese.

In September 2008, ATSDR released a Toxicological Profile for Manganese (Update) for public comment. This profile updated the previous manganese profile that was released in 2000. In this update, ATSDR derived a chronic-duration inhalation MRL for inorganic manganese of 0.3 µg manganese/m^3 of air (manganese in respirable dust). Using a study by Roels et al. (1992), this MRL was based on a $BMCL_{10}$ of 142 µg manganese/m^3 for neurological effects which was adjusted to a continuous exposure basis and divided by an uncertainty factor of 100 (10 for human variability; and 10 for limitations/deficiencies in the database).

Based upon public comments, as well as, peer review and interagency and intraagency comments, this chronic-duration inhalation MRL is being reevaluated. Because of these ongoing considerations, the Agency has elected to retain the chronic inhalation MRL of 0.04 µg manganese/m^3 that was derived in 2000 Toxicological Profile for Manganese (as described in the attached MRL worksheet) until such time as the profile is finalized.

The 2000 ATSDR Toxicological Profile for Manganese derived a chronic inhalation MRL for inorganic manganese of 0.04 µg manganese/m^3 (manganese in respirable dust) based on a $BMCL_{10}$ of 74 µg manganese/m^3 (manganese in respirable dust) for abnormal performance in tests of hand steadiness, eye-hand coordination, or reaction time in a study of 92 male workers in a dry alkaline battery plant (Roels et al. 1992). The MRL was derived by adjustment of the $BMCL_{10}$ to a continuous exposure basis and dividing by an uncertainty factor of 500 (10 for human variability; 10 for database deficiencies and limitations; and a modifying factor of 5 for potentially increased susceptibility in children based on differential pharmacokinetics in the young).

Roels et al. (1992) was used as the critical study in both the 2000 and 2008 manganese assessments. The 2008 Toxicological Profile for Manganese- Draft for Public Comment in deriving its chronic inhalation MRL of 0.3 µg manganese/m^3 did not use a modifying factor of 5 for potentially increased susceptibility in children. Assessors initially concluded that the uncertainty factor of 10 which was applied for human variability would provide sufficient protection for differential kinetics in children compared to adults. However, a number of additional, potentially susceptible populations were identified, including neonates, the elderly, pregnant women, alcoholics, and the malnourished. Because of these concerns, it was decided that the MRL of 0.04 µg manganese/m^3 that was derived in the 2000 Toxicological Profile for Manganese would be retained as the chronic inhalation MRL because it utilized an additional modifying factor of 5 for potentially increased susceptibility in children, as well as other, potentially susceptible populations.

Reference Concentration (RfC)/Environmental Protection Agency (EPA)

EPA derived a chronic inhalation RfC of 5×10^{-5} mg/m^3 for respirable manganese (IRIS 2008), equivalent to 0.05 µg/m^3. This value is based on the neurological LOAEL of 0.15 mg/m^3 from the same study of battery workers exposed to manganese dioxide (Roels et al. 1992) that was used as the critical study for the chronic inhalation MRL. The LOAEL was calculated by dividing the geometric mean concentration of the lifetime-integrated respirable dust concentration for the exposed workers by the average duration of employment in the facility. EPA calculated the RfC by adjusting the LOAEL of 0.15 mg manganese/m^3 for continuous exposure and dividing by an uncertainty factor of 1000 (10 for use of a LOAEL; 10 for human variability; 10 for database limitations).

Reference Concentration/Health Canada
Health Canada (2008) determined reference concentrations ranging from 0.05 to 0.08 µg manganese/m^3. In this assessment, benchmark dose analyses were conducted on data for neurobehavioral end points from a study of manganese alloy workers by Lucchini et al. (1999). Using the average manganese concentrations in respirable dust over the 5-year period before testing as the dose metric, dose-response data for six tests of fine motor control, two aspects of memory tests, and one test of mental arithmetic were fit to linear models, which were used to calculate $BMCL_{05}$ values ranging from about 0.019 to 0.0588 mg manganese/m^3. After adjustment to convert from occupational exposure (5 days/week, 8 hours/24 hours) to continuous exposure, adjusted $BMCL_{05}$ values were divided by a total uncertainty factor of 100 to arrive at reference concentrations. The uncertainty factor was comprised of a factor of 10 for human variability and a second factor of 10 to account for limitations/deficiencies in the database.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Manganese
CAS Number: 7439-96-5
Profile Status: Toxicological Profile for Manganese (1999)
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key:
Species: Human

Minimal Risk Level: 0.00004 mg manganese/m^3

Reference: Roels H, Ghyselen P, Buchet JP. 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49:25-34.

Experimental design: Neurological effects of manganese exposure were evaluated in 92 male workers in a dry alkaline battery factory. The control group was 101 age- and area-matched workers not occupationally exposed to manganese but with similar work schedules and workloads. Workers were exposed an average duration of 5.3 years (range 0.2-17.7 years) to average (geometric mean) concentrations of 215 μg manganese/m^3 and 948 μg manganese/m^3 in respirable and total dust, respectively. The authors noted that the work processes had not changed significantly in the last 15 years, indicating that past exposures should be comparable to those measured in the study. Neurological function was measured using an audioverbal short term memory test, a simple visual reaction time test using a chronoscope, and three manual tests of hand steadiness, coordination, and dexterity. This report provided good documentation of individual exposure data and characterization of the population studied.

Effects noted in study and corresponding doses: Manganese-exposed workers performed significantly worse than the controls on the neurobehavioral tests, with particular differences in simple reaction time, eye-hand coordination, and hand steadiness. The authors provided their data on the manganese-exposed group evaluated in this study. These data included individual exposure levels and whether the individual had an abnormal performance in the neurobehavioral tests. A dose-response curve was constructed using benchmark dose analysis (BMD) of these data. From this plot a lower 95% confidence limit was estimated around the level of manganese exposure expected to result in a 10% response rate, the $BMDL_{10}$, which was considered an acceptable surrogate for a NOAEL. The authors note the data do not provide a clear-cut dose-effect relationship.

Dose and endpoint used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] Other $BMDL_{10}$ of 74 μg manganese/m^3

Conversion to Continuous Exposure:

[X] 5/7 to account for intermittent exposure (5 days per week)
[X] 8/24 to account for intermittent exposure (8 hours per day)

Uncertainty and Modifying Factors used in MRL derivation:

[X] 10 for human variability
[ ] 10 for the use of a LOAEL
[X] 10 for the potential for differences in toxicity from different manganese forms and other limitations in the database for inhalation exposures, including lack of data on developmental effects and reproductive effects in females
[X] 5 for modifying factor for potentially increased susceptibility in children based on differential pharmacokinetics in the young

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
NA

Other additional studies or pertinent information which lend support to this MRL:

Dr. Anders Iregren also provided individual data on total manganese exposure and performance on neurobehavioral tests for the occupational cohort that participated in his study (Iregren 1990; Wennberg et al. 1991). A benchmark dose analysis was also performed with these data under contract with ATSDR (Clewell and Crump 1999) and the $BMDL_{10}$ value derived from this evaluation was 0.071 mg manganese/m^3 based upon the reported observation that the respirable fraction ranged upwards to 80% of the total dust measured. This $BMDL_{10}$ value is essentially the same as that estimated for the Roels et al. (1992) study, thus giving support to the value obtained for the current MRL study. More recently, Gibbs et al. (1999) reported that exposure to 0.051 mg manganese/m^3 (median, respirable manganese) was a NOAEL among workers at a metal producing plant when evaluated using both novel and older neurobehavioral test methods. However, individual exposure and test performance data from this study were not available to ATSDR for conducting a benchmark dose analysis. Nonetheless, the NOAEL reported by Gibbs et al. (1999) is consistent with the $BMDL_{10}$ values derived from raw data provided by Drs. Roels and Iregren. Several epidemiological studies also report preclinical neurological effects and support the Roels et al. (1992) and Iregren (1990) studies. An older study by Roels et al. (1987a) involved workers chronically exposed to manganese dusts at a concentration of 1 mg/m^3 in a factory using manganese oxides and salts. The authors noted a slight increase in frequency of weakness and tremor, and decreased scores on psychomotor tests (eye-hand coordination, hand steadiness, short-term memory, simple reaction time). In this study the exposure concentration did not distinguish between respirable dust and nonrespirable dust. In a recent study by Mergler et al. (1994), 145 workers from a ferromanganese and silicomanganese alloy factory were observed for adverse effects from exposure to manganese dusts. Environmental levels of total manganese in dust were measured at 0.014-11.48 mg/m^3 (median 0.151 mg/m^3, mean 1.186 mg/m^3). Mean duration of exposure was 16.7 years. Manganese workers showed decreased performance on tests of motor function, had difficulty in set shifting, and exhibited significantly lower levels of cognitive flexibility. Lucchini et al. (1995) reported neurobehavioral effects in 58 workers exposed to manganese dusts for 1–28 years (mean, 13 years). These workers were observed during a period of forced cessation from work and exhibited decreased neurobehavioral performance (finger tapping, symbol digit, digit span, and additions tests). Environmental levels of total dust ranged from 0.027–0.27 mg/m^3 (geometric means), with respirable dust given as 50–60% of the total dust. A recent study in occupational workers in a ferroalloy plant reported decreased performance in neurobehavioral tests (e.g., symbol digit; finger tapping, dominant and non-dominant hand; digit span) was correlated with the CEI of workers who were employed in high, medium, or low-exposure areas. While airborne manganese concentrations were correlated with blood and urine manganese levels, CEI values were not (Lucchini et al. 1999). In a longitudinal follow-up study, Roels and colleagues observed that manganese concentrations were directly, and inversely, correlated with performance on a test measuring eye-hand coordination in a population of exposed workers at a dry-alkaline battery plant Roels et al. (1999). These workers were employed during a time of decreasing concentrations of airborne manganese as described in the following subgroups: low (~0.31–0.16 mg/m^3), medium (~0.90–0.250 mg/m^3), and high-exposure (~3.00–1.20 mg/m^3). Visual reaction time and hand steadiness tests did not reveal improved performance when manganese concentrations decreased. Further, increased performance by the medium- and high-exposure groups on the eye-hand coordination test during the period of lowest manganese exposure still did not reach the level of the control population, thus suggesting a permanent neurological effect from manganese exposures at these levels